Complete Summary

GUIDELINE TITLE

DR-TB and HIV infection. In: Guidelines for the programmatic management of drug-resistant tuberculosis.

BIBLIOGRAPHIC SOURCE(S)

DR-TB and HIV infection. In: World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: World Health Organization (WHO); 2008. p. 89-106. [44 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Drug-resistant tuberculosis (DR-TB) and human immunodeficiency virus (HIV) coinfection, including:

- Multidrug-resistant tuberculosis (MDR-TB)
- Extensively drug-resistant tuberculosis (XDR-TB)

GUIDELINE CATEGORY

Counseling
Diagnosis
Evaluation
Management

Prevention
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine

INTENDED USERS

Advanced Practice Nurses
Clinical Laboratory Personnel
Health Care Providers
Health Plans
Hospitals
Managed Care Organizations
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To illustrate where the management of drug-resistant tuberculosis (DR-TB) differs in the presence of known or suspected human immunodeficiency virus (HIV) infection and to provide guidance on recent developments in the approach to TB/HIV
- To disseminate consistent, up-to-date recommendations for the diagnosis and management of multidrug-resistant tuberculosis in a variety of geographical, political, economic and social settings
- To enable access to comprehensive, up-to-date, technical and clinical information on the prevention and management of DR-TB and to encourage the implementation of known best practice
- To assist in the development of national policies to improve the DR-TB

TARGET POPULATION

Patients with known or suspected drug-resistant tuberculosis (DR-TB) in association with human immunodeficiency virus (HIV) infection

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Treatment/Management

1. Perform provider-initiated human immunodeficiency virus (HIV) testing and counseling
2. Use standard algorithms to diagnose pulmonary and extrapulmonary TB
3. Use mycobacterial cultures and rapid diagnostic procedures
4. Perform drug susceptibility testing (DST)

5. Determine the extent (or prevalence) of TB drug resistance in patients with HIV
6. Introduce antiretroviral therapy (ART) promptly in drug-resistant tuberculosis (DR-TB)/HIV patients
7. Consider empirical therapy with second-line antituberculosis drugs
8. Provide co-trimoxazole preventive therapy for patients with active TB and HIV
9. Arrange treatment follow-up by a specialized team
10. Implement additional nutritional and socioeconomic support
11. Ensure effective infection control
12. Involve key stakeholders in DR-TB/HIV activities
13. Monitor for overlying toxicity with ART and DR-TB therapy

MAJOR OUTCOMES CONSIDERED

- Incidence of drug-resistant tuberculosis (DR-TB) and human immunodeficiency virus (HIV) co-infection
- Rate of transmission
- Frequency of adverse reactions to combination therapy
- Rate of nonadherence
- Incidence of immune reconstitution inflammatory syndrome (IRIS)
- Mortality

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The nominated lead author for each chapter used a limited evidence retrieval consisting of:

- Personal collection of publications and case reports
- Literatures searches using PubMed and other databases and search engines
- Existing guidelines, both from World Health Organizaiton (WHO) and from other internationally recognized organizations
- Expert consensus during several group meetings for specific topics
- Unpublished data, for example data supplied to the Green Light Committee by their approved multidrug-resistant tuberculosis (MDR-TB) management projects

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus
Subjective Review

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The evidence was synthesized by each lead author, but a formal quality assessment was not used. Given the relatively small field of experts in managing drug-resistant tuberculosis, expert opinion was sought from several of the original researchers in the field. The evidence was not formally assessed or graded and there are no formal evidence summaries.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

A meeting of the World Health Organization (WHO) Guidelines Steering Group, together with several WHO advisers who had contributed to the 2006 edition, took place in April 2006. It was agreed that there was an urgent need for guidance on the best response to extensively drug-resistant tuberculosis (XDR-TB), based on the emerging evidence. The group identified the chapters to be reconsidered and the gaps to be addressed in this emergency update.

Of the total 18 chapters in the original guideline document, eight have been reviewed and substantially changed in response to the emerging evidence about multidrug-resistant tuberculosis and XDR-TB (chapters 1, 4, 5, 6, 7, 10, 12 and 18). One chapter is new (Chapter 19). The remaining chapters have undergone minor revisions to ensure consistency but have not been rewritten or had any new evidence included.

There was also a decision that a full review of the Guidelines will be started after the emergency update. The WHO Guidelines Review Committee was in place by January 2008 and had already developed draft Guidance for Emergency Guidelines which was used to guide best practice in the finalization of this emergency update.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Cost is not explicitly considered as part of the recommendations, although the realities of human resources, socioeconomic issues and health system infrastructure are taken into consideration throughout the original guideline document.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The chapters were each reviewed by at least one, and usually several, members of the Guidelines Reference Group, from both within the World Health Organization (WHO) Stop tuberculosis (TB) and human immunodeficiency virus (HIV) departments and outside external experts, as appropriate. One of the expert advisers on the Steering Group was commissioned to harmonize and review all the updated chapters. The remainder of the Steering Group also reviewed the whole document and provided extensive and detailed feedback.

The first draft of the guidelines was reviewed by the Steering Group at meeting held in February 2008. Other advisers at this meeting were Dr Malgosia Grzemska (WHO), Dr Suzanne Hill (WHO), Dr Tim Holtz (CDC, USA) and Dr Kathrin Thomas (WHO). Any outstanding issues were then resolved by e-mail to agree the final version. Other members of the group were asked to provide reviews at these later stages for particular issues.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Key Changes for the Emergency Update 2008 Compared to the 2006 Guideline

- Stronger emphasis is placed on performing drug susceptibility testing (DST) of human immunodeficiency virus (HIV)-infected individuals at the start of anti-tuberculosis (TB) therapy in areas of moderate or high multidrug-resistant TB (MDR-TB) prevalence. This subject is also introduced in the National Guideline Clearinghouse (NGC) summary of the World Health Organization (WHO) guideline, Case-finding strategies, as a key change.
- Greater detail is provided on the concomitant treatment of HIV and MDR-TB, including discussion of immune reconstitution inflammatory syndrome (IRIS).
- Table 3, below, provides a list of potential overlapping and additive toxicities of antiretroviral therapy (ART) and anti-TB therapy.

Key Recommendations (*Indicates updated recommendation)

- Perform provider-initiated HIV testing and counselling in all TB suspects.*
- Use standard algorithms to diagnose pulmonary and extrapulmonary TB.
- Use mycobacterial cultures and, where available, newer more rapid methods of diagnosis.

- Perform DST at the start of antituberculosis therapy to avoid mortality due to unrecognized drug-resistant tuberculosis (DR-TB) in HIV-infected individuals.*
- Determine the extent (or prevalence) of antituberculosis drug resistance in patients with HIV.
- Introduce antiretroviral therapy promptly in DR-TB/HIV patients.
- Consider empirical therapy with second-line antituberculosis drugs.*
- Provide co-trimoxazole preventive therapy (CPT) as part of a comprehensive package of HIV care to patients with active TB and HIV.*
- Arrange treatment follow-up by a specialized team.
- Implement additional nutritional and socioeconomic support.
- Ensure effective infection control.
- Involve key stakeholders in DR-TB/HIV control activities.
- Monitor for overlying toxicity with ART and DR-TB therapy.

General Considerations

Early diagnosis of DR-TB and HIV, prompt treatment with adequate regimens, sound patient support and strong infection control measures are all essential components in the management of DR-TB in HIV-infected people.

Recommended Collaborative TB/HIV Activities

WHO recommends that certain collaborative activities are carried out to decrease the joint burden of TB and HIV (see Table 1, below).

These activities are the backbone of the WHO TB/HIV collaborative strategy that, along with the implementation of effective directly observed therapy-short course (DOTS) programmes, will strengthen and increase the success of DR-TB/HIV control and treatment activities.

These guidelines recommend whenever possible the highest standard of care. The activities described below are based on the TB/HIV activities listed in Table 1 and are adapted to be specifically applicable to DR-TB.

- **Perform provider-initiated HIV testing and counselling in all TB suspects**. Given the high levels of HIV and TB coinfection in many settings, provider-initiated HIV counselling and testing is recommended for all TB suspects. Provider-initiated testing can be done at the same time the sputum is sent for smear microscopy (or culture). This is more efficient and more likely to be successful than referring patients elsewhere for HIV testing and counseling. Provider-initiated counselling and testing can serve as a gateway to lifesaving prevention, care and treatment interventions.
- **Use standard algorithms to diagnose pulmonary and extrapulmonary TB**. New recommendations for improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary TB have been put forth by WHO. Also see Clinical Features and Diagnosis of DR-TB in HIV-Infected Patients, below.
- **Use mycobacterial cultures and, where available, newer more rapid methods of diagnosis**. Mycobacterial cultures of sputum or other fluids and tissues are recommended to help in the diagnosis of sputum smear-negative and extrapulmonary TB. The heavy reliance on smear microscopy has

significant limitations and is insufficient to reliably diagnose a significant proportion of HIV-coinfected patients, especially as the degree of immunosuppression advances. Rapid methods such as liquid culture or molecular techniques should be considered. See the NGC summary of the WHO guideline, Laboratory aspects, for more information on culture methods.

- **Perform DST at the start of antituberculosis therapy**. Unrecognized DR-TB carries a high risk of mortality in patients with HIV. Prompt initiation of appropriate antituberculosis treatment (and subsequent initiation of antiretroviral therapy [ART]) can reduce mortality among HIV-infected patients infected with DR-TB. Because unrecognized MDR-TB and XDR-TB are associated with such high mortality in HIV-infected patients, many international protocols dictate the performance of DST and/or rapid drug-resistance testing for all HIV-infected patients with established active TB. (See the NCG summary of the WHO guideline, Case-finding strategies, and "Clinical Features and Diagnosis of DR-TB in HIV-Infected Patients" below for more discussion on rapid tests and diagnosing DR-TB in HIV patients.) While performing DST for all TB/HIV coinfected patients is the standard of care for many areas, these guidelines recognize that this may be difficult or impossible in many resource-limited settings. Alternative strategies are provided in "Clinical Features and Diagnosis of DR-TB in HIV-Infected Patients" below, for programmes with resource constraints. However, universal access to DST is the long-term goal for all settings.
- **Determine the extent (or prevalence) of TB drug resistance in patients with HIV**. Programmes should determine the extent of the overlap of the DR-TB and HIV epidemics. This can be done in two ways: (i) data from population-based TB drug resistance surveillance (DRS) can be linked with HIV testing of those TB patients included; and/or (ii) when implementing HIV surveillance among TB patients (or provider-initiated testing and counselling for all TB patients), DST can be included in all, or an unbiased sub-set of, HIV-infected patients. The latter technique is more complex if rates of DR-TB in HIV-infected and negative patients are to be compared, as a control group of HIV-negative TB infected patients would also need to be established.
- **Introduce ART promptly in DR-TB/HIV patients**. These guidelines recommend the prompt initiation of ART in HIV-infected patients with DR-TB according to WHO guidelines (see "Concomitant Treatment of DR-TB and HIV" and Table 2 below, on when to initiate HIV treatment in DR-TB). Where indicated, protocols to manage immune reconstitution inflammatory syndrome (IRIS) should be followed (see "Immune Reconstitution Inflammatory Syndrome" below, for more information on IRIS).
- **Consider empirical therapy with second-line antituberculosis drugs**. Patients with a very high risk of DR-TB can be empirically started on Category IV regimens. This strategy can be applied to all patients regardless of HIV status but is especially important in those with HIV. (Note: empirical use of Category IV is reserved for patients who have an extremely high rate of MDR-TB, such as failures of Category II or very close contacts of DR-TB. See the NGC summary of the WHO guideline, Case-finding strategies, for more information on the use of empirical Category IV).
- **Provide CPT for patients with active TB and HIV**. CPT should be provided to all patients with HIV according to WHO recommendations. This therapy is not known to interact significantly with any of the second-line antituberculosis agents. There are overlapping toxicities between ART, antituberculosis therapy and CPT, and vigilance in terms of monitoring adverse effects is required (see Table 3 below and the NGC summary of the WHO guideline,

Initial evaluation, monitoring of treatment and management of adverse effects).

- **Arrange treatment follow-up by a specialized team**. The team of care providers should be familiar with the treatment of both DR-TB and HIV, with close monitoring of potential additive adverse effects and nutritional status as well as periodic assessments of therapeutic response for both infections.
- **Implement additional nutritional and socioeconomic support**. Patients with DR-TB and HIV may suffer from severe wasting, diarrhoeal diseases, and malabsorption syndromes. Coinfected patients often come from socially marginalized groups or from families with low economic resources. Additionally, DR-TB therapy with second-line antituberculosis medications may result in adverse effects that affect treatment adherence and require more frequent visits to health facilities. Wherever possible, patients with DR-TB/HIV and limited means should be offered socioeconomic and nutritional support (also see the NGC summary of the WHO guideline, Treatment delivery and community-based DR-TB support, for more information on treatment support).
- **Ensure effective infection control**. Infection control procedures can reduce the risk of *Mycobacterium tuberculosis* transmission in HIV/AIDS care facilities. Infection control issues concerning DR-TB, including issues regarding HIV, are discussed in the NGC summary of the WHO guideline, Drug resistance and infection control, and in other documents published by WHO.
- **Involve key stakeholders in DR-TB/HIV activities**. The local/national TB/HIV coordinating bodies, community groups and key stakeholders should be involved in the planning and monitoring of DR-TB/HIV activities and programmes.

Table 1. WHO-Recommended Collaborative TB/HIV Activities*

A. ESTABLISH THE MECHANISMS FOR COLLABORATION
A. Â Â Â 1. Set up a coordinating body for TB/HIV activities effective at all levels
A. Â Â Â 2. Conduct surveillance of HIV prevalence among TB patients
A. Â Â Â 3. Carry out joint TB/HIV planning
A. Â Â Â 4. Conduct monitoring and evaluation
B. DECREASE THE BURDEN OF TB IN PEOPLE LIVING WITH HIV/AIDS
B. Â Â Â 1. Establish intensified TB case-finding and contact tracing
B. Â Â Â 2. Introduce isoniazid preventive therapy
B. Â Â Â 3. Ensure TB infection control in health-care and congregate settings
C. DECREASE THE BURDEN OF HIV IN TB PATIENTS
C. Â Â Â 1. Provide HIV testing and counselling
C. Â Â Â 2. Introduce HIV prevention methods

C. Â Â Â 3. Introduce co-trimoxazole preventive therapy

C. Â Â Â 4. Ensure HIV/AIDS care and support

C. Â Â Â 5. Introduce antiretroviral therapy

*A detailed description of each of the activities listed in the table can be found in the WHO document *Interim policy on collaborative TB/HIV activities* (2004).

Clinical Features and Diagnosis of DR-TB in HIV-Infected Patients

For patients with advanced HIV disease, mycobacterial culture of other fluids (e.g., blood, pleural fluid, ascitic fluid, cerebrospinal fluid and bone-marrow aspirates) and histopathology (e.g., lymph node biopsies) may be helpful in diagnosis.

In many programmes and areas, all HIV patients with TB are screened for drug-resistance with DST. Rapid drug-resistance testing is the DST technique of choice since this allows prompt diagnosis of MDR-TB, decreasing the time the patient may be on an inadequate regimen and the period during which the patient may be spreading DR-TB.

Programmes without facilities or resources to screen all HIV-infected patients for DR-TB should put significant efforts into obtaining them, especially if DR-TB rates are moderate or high. Some programmes may adopt a strategy of targeted DST for patients with increased risk of DR-TB (such as those in whom treatment has failed or who are contacts of DR-TB cases (see the NGC summary of the WHO guideline, Case-finding strategies). Programmes may also choose to use targeted DST for those with lower CD4 counts (e.g., less than 200 cells/mm^3) since these patents are at a very high risk of death due to unrecognized DR-TB.

Concomitant Treatment of DR-TB and HIV

The treatment of DR-TB in patients with HIV is very similar to that in patients without HIV and is described in the NGC summary of the WHO guideline, Treatment strategies for MDR-TB and XDR-TB, with the following exceptions:

- ART plays a crucial role, as mortality in MDR-TB/HIV patients without the use of ART is extremely high (91–100% as reported in one analysis of MDR-TB outbreaks in 9 different institutions).
- Adverse effects are more common in patients with HIV. The multiple medicines involved in DR-TB with recognized high toxicity risks, often combined with ART, results in a high incidence of adverse effects. Some toxicities are common to both antituberculosis treatment and ART, which may result in added rates of adverse events.
- Monitoring needs to be more intense for both response to therapy and adverse effects.
- The use of thioacetazone is not recommended for patients with HIV or for routine use in populations with high rates of HIV.
- IRIS may complicate therapy.

Initiating ART Treatment in Patients with DR-TB

The optimal timing for the introduction of ART in patients receiving TB treatment is unknown. Table 2, based on WHO guidelines for the treatment of HIV infection in adults and adolescents, provides recommendations for initiating ART in relationship to starting therapy for DR-TB.

Table 2. Timing of ART in the ART-Naive Patient Starting Antituberculosis Therapy for DR-TB

CD4 Cell Count	ART Recommendations	Timing of ART in Relation to Start of DR-TB Treatment
CD4 <200 cells/mm^3	Recommend ART	At two weeks or as soon as DR-TB treatment is tolerated
CD4 between 200 and 350 cells/mm^3	Recommend ART	After eight weeks*
CD4 >350 cells/mm^3	Defer ART**	Re-evaluate patient monthly for consideration of ART start. CD4 testing is recommended every three months during DR-TB treatment.
Not available	Recommend ART***	Between two and eight weeks

*Clinical evaluation may prompt earlier initiation of ART.

**ART should be started if other non-TB stage 3 or 4 events are present.

***This recognizes that some patients may be prematurely placed on life-long ART.

DR-TB in Patients Already Receiving ART

There are two issues to consider in patients who are diagnosed with DR-TB while on ART. The first is whether modification of ART is needed due to drug–drug interactions or to decrease the potential of overlapping toxicities. These concerns are discussed below.

The second issue is whether the presentation of active DR-TB in a patient on ART constitutes ART failure. The principles of determining failure in such cases are described in other WHO documents (available at http://www.who.int/entity/hiv/pub/guidelines/adult/en/index.html). If ART failure has been diagnosed, it is not recommended to begin a new second-line ART regimen at the same time as initiation of a DR-TB regimen. Instead, continue the present ART regimen and switch to the second-line ART regimen 2–8 weeks after the start of DR-TB treatment.

Important Drug–Drug Interactions in the Treatment of HIV and DR-TB

Currently, little is known about drug–drug interactions between second-line antituberculosis agents and antiretroviral therapy. There are several known interactions between drugs used to treat HIV and TB, which are summarized below.

- **Rifamycin derivatives**. While rifamycin derivatives are not routinely used in DR-TB treatment, they are used in the treatment of rifampicin-sensitive poly- and mono-resistant TB.
- **Quinolones and didanosine**. Buffered didanosine contains an aluminium/magnesium-based antacid and, if given jointly with fluoroquinolones, may result in decreased fluoroquinolone absorption; it should be avoided, but if it is necessary it should be given six hours before or two hours after fluoroquinolone administration. The enteric coated (EC) formulation of didanosine can be used concomitantly without this precaution.
- **Ethionamide/protionamide**. Based on limited existing information of the metabolism of the thionamides (ethionamide and protionamide), this drug class may have interactions with antiretroviral drugs. Ethionamide/protionamide is thought to be metabolized by the CYP450 system, although it is not known which of the CYP enzymes are responsible. Whether doses of ethionamide/protionamide and/or certain antiretroviral drugs should be modified during the concomitant treatment of DR-TB and HIV is completely unknown.
- **Clarithromycin**. Clarithromycin is a substrate and inhibitor of CYP3A and has multiple drug interactions with protease inhibitors (PIs) and nonnucleotide reverse transcriptase inhibitors (NNRTIs). If possible, the use of clarithromycin should be avoided in patients coinfected with DR-TB and HIV because of both its weak efficacy against DR-TB and multiple drug interactions.

Potential Drug Toxicity in the Treatment of HIV and DR-TB

There is limited evidence on the frequency and severity of toxicities and adverse events from ART and second-line antituberculosis therapy. In general, HIV patients have a higher rate of adverse drug reactions to both TB and non-TB medications, and the risk of adverse drug reactions increases with the degree of immunosuppression. Identifying the source of adverse effects in patients receiving concomitant therapy for DR-TB and HIV is difficult. Many of the medications used to treat DR-TB and HIV have overlapping, or in some cases additive, toxicities. Often, it may not be possible to link adverse effects to a single drug, as the risk of resistance for ART therapy precludes the typical medical challenge of stopping all medications and starting them one by one.

Adverse effects that are common to both antiretroviral and antituberculosis drugs are listed in Table 3. It should be noted that relatively very little is known about the rates of adverse effects in the concomitant treatment of DR-TB and HIV. Table 3 is meant to alert the clinician to potentially overlapping and additive toxicities, and as of the writing of these guidelines is based on preliminary, non-published data and expert opinion.

When possible, avoid the use of agents with shared adverse effect profiles. Often, however, the benefit of using drugs that have overlying toxicities outweighs the risk. Therefore, if two drugs with overlapping toxicities are determined to be

essential in a patient's regimen, these guidelines recommend increased monitoring of adverse effects rather than disallowing a certain combination. See the NGC summary of the WHO guideline, Initial evaluation, monitoring of treatment and management of adverse effects, and "Monitoring of DR-TB and HIV Therapy in Coinfected Patients," below, for monitoring adverse effects in HIV-infected patients.

Table 3. Potential Overlying and Additive Toxicities of ART and Antituberculosis Therapy

Drugs that are more strongly associated with adverse effects appear in bold.

Toxicity	Antiretroviral Agent	Antituberculosis Agent	Comments
Peripheral neuropathy	**D4T**, **ddI**, **ddC**	**Lzd**, **Cs**, **H**, Amino glycosides, Eto/Pto, E	Avoid use of D4T, ddI and ddC in combination with Cs or Lzd because of theoretically increased peripheral neuropathy. If these agents must be used and peripheral neuropathy develops, replace the ARV agent with a less neurotoxic agent and treat according to the NGC summary of the WHO guideline, Initial evaluation, monitoring of treatment and management of adverse effects.
Central nervous system (CNS) toxicity	**EFV**	**Cs**, H, Eto/Pto, Fluoroquinolones	Efavirenz has a high rate of CNS adverse effects (confusion, impaired concentration, depersonalization, abnormal dreams, insomnia and dizziness) in the first 2–3 weeks, which typically resolve on their own. If these effects do not resolve on their own, consider substitution of the agent. At present, there are limited data on the use of EFV with Cs; concurrent use is accepted practice with frequent monitoring for

Drugs that are more strongly associated with adverse effects appear in bold.			
Toxicity	**Antiretroviral Agent**	**Antituberculosis Agent**	**Comments**
			CNS toxicity. Frank psychosis is rare with EFV alone.
Depression	**EFV**	**Cs**, Fluoroquinolones, H, Eto/Pto	Severe depression can be seen in 2.4% of patients receiving EFV.* Consider substituting for EFV if severe depression develops. The severe socioeconomic circumstances of many patients with chronic disease can also contribute to depression.
Headache	**AZT**, **EFV**	**Cs**	Rule out more serious causes of headache such as bacterial meningitis, cryptococcal meningitis, CNS toxoplasmosis, etc. Use of analgesics (ibuprofen, paracetamol) and good hydration may help. Headache secondary to AZT, EFV and Cs is usually self-limited.
Nausea and vomiting	**RTV**, **D4T**, NVP, and most others	**Eto/Pto, PAS, H, E, Z** and others	Nausea and vomiting are common adverse effects and can be managed with modalities described in the NGC summary of the WHO guideline, Initial evaluation, monitoring of treatment and management of adverse effects. Persistent vomiting and abdominal pain may be a result of developing lactic acidosis and/or hepatitis secondary to medications.
Abdominal pain	**All ART treatment has**	**Cfz**, **Eto/Pto**, **pAS**	Abdominal pain is a common adverse effect

Drugs that are more strongly associated with adverse effects appear in bold.			
Toxicity	**Antiretroviral Agent**	**Antituberculosis Agent**	**Comments**
	been associated with abdominal pain		and often benign; however, abdominal pain may be an early symptom of severe adverse effects such as pancreatitis, hepatitis or lactic acidosis.
Pancreatitis	**D4T**, **ddI**, **ddC**	**Lzd**	Avoid use of these agents together. If an agent causes pancreatitis suspend it permanently and do not use any of the pancreatitis producing anti-HIV medications (D4T, ddI, or ddC) in the future. Also consider gallstones or alcohol as a potential cause of pancreatitis.
Diarrhea	**All protease inhibitors, ddI (buffered formula)**	**Eto/Pto**, **PAS**, Fluoroquinolones	Diarrhoea is a common adverse effect. Also consider opportunistic infections as a cause of diarrhoea, or clostridium difficile (a cause of pseudomembranous colitis).
Hepatotoxicity	**NVP, EFV, all protease inhibitors** (RTV > other protease inhibitors), **all NRTIs**	**H**, **R**, **E**, **Z**, PAS, Eto/Pto, Fluoroquinolones	Follow hepatotoxicity treatment recommendations in the NGC summary of the WHO guideline Initial evaluation, monitoring of treatment and management of adverse effects. Also consider TMP/SMX as a cause of hepatotoxicity if the patient is receiving this medication. Also rule out viral etiologies as cause of hepatitis (Hepatitis A, B, C, and CMV).
Skin rash	**ABC**, **NVP**,	**H**, **R**, **Z**, **PAS**,	Do not re-challenge with

Drugs that are more strongly associated with adverse effects appear in bold.			
Toxicity	**Antiretroviral Agent**	**Antituberculosis Agent**	**Comments**
	EFV, **D4T** and others	Fluoroquinolones, and others	ABC (can result in life-threatening anaphylaxis). Do not re-challenge with an agent that caused Stevens-Johnson syndrome. Also consider TMP/SMX as a cause of skin rash if the patient is receiving this medication. Thioacetazone is contraindicated in HIV because of life-threatening rash.
Lactic acidosis	**D4T**, **ddI**, **AZT**, **3TC**	**Lzd**	If an agent causes lactic acidosis, replace it with an agent less likely to cause lactic acidosis.
Renal toxicity	TDF (rare)	**Aminoglycosides**, **Cm**	TDF may cause renal injury with the characteristic features of Fanconi syndrome, hypophosphataemia, hypouricaemia, proteinuria, normoglycaemic glycosuria and, in some cases, acute renal failure. There are no data on the concurrent use of TDF with aminoglycosides or Cm. Use TDF with caution in patients receiving aminoglycosides or Cm. Even without the concurrent use of TDF, HIV-infected patients have an increased risk of renal toxicity secondary to aminoglycosides and Cm. Frequent creatinine and electrolyte monitoring every 1 to 3 weeks is recommended (see the NGC summary of the WHO guideline Initial

Drugs that are more strongly associated with adverse effects appear in bold.			
Toxicity	**Antiretroviral Agent**	**Antituberculosis Agent**	**Comments**
			evaluation, monitoring of treatment and management of adverse effects). Many ARV and antituberculosis medications need to be dose adjusted for renal insufficiency.
Nephrolithiasis	**IDV**	None	No overlapping toxicities regarding nephrolithiasis have been documented between ART and antituberculosis medications. Adequate hydration prevents nephrolithiasis in patients taking IDV. If nephrolithiasis develops while on IDV, substitute with another protease inhibitor if possible.
Electrolyte disturbances	TDF (rare)	**Cm**, **Aminoglycosides**	Diarrhoea and/or vomiting can contribute to electrolyte disturbances. Even without the concurrent use of TDF, HIV-infected patients have an increased risk of both renal toxicity and electrolyte disturbances secondary to aminoglycosides and Cm.
Bone marrow suppression	AZT	**Lzd**, R, Rfb, H	Monitor blood counts regularly (see the NGC summary of the WHO guideline, Initial evaluation, monitoring of treatment and management of adverse effects). Replace AZT if bone marrow suppression develops. Consider

Drugs that are more strongly associated with adverse effects appear in bold.			
Toxicity	**Antiretroviral Agent**	**Antituberculosis Agent**	**Comments**
			suspension of Lzd. Also consider TMP/SMX as a cause if the patient is receiving this medication. Consider adding folinic acid supplements, especially if receiving TMP/SMX.
Optic neuritis	ddI	**E**, Eto/Pto (rare)	Suspend agent responsible for optic neuritis permanently and replace with an agent that does not cause optic neuritis.
Hyperlipidemia	**protease inhibitors**, **EFV**	None	No overlapping toxicities regarding hyperlipidemia have been documented between ART and antituberculosis medications. Follow WHO ART guidelines for management of hyperlipidemia.
Lipodystrophy	**NRTIs** (especially D4T and ddI)	None	No overlapping toxicities regarding lipodystrophy have been documented between ART and antituberculosis medications. Follow WHO ART guidelines for management of lipodystrophy.
Dysglycemia (disturbed blood sugar regulation)	**Protease inhibitors**	**Gfx**, Eto/Pto	Protease inhibitors tend to cause insulin resistance and hyperglycaemia. Eto/Pto tend to make insulin control in diabetics more difficult, and can result in hypoglycaemia and poor glucose regulation. Gatifloxacin is

Drugs that are more strongly associated with adverse effects appear in bold.			
Toxicity	**Antiretroviral Agent**	**Antituberculosis Agent**	**Comments**
			no longer recommended by the GLC for use in treatment of TB because of this side-effect.
Hypothyroidism	D4T	**Eto/pto**, **PAS**	There is potential for overlying toxicity, but evidence is mixed. Several studies show subclinical hypothyroidism associated with HAART, particularly stavudine. PAS and Eto/Pto, especially in combination, can commonly cause hypothyroidism.

Abbreviations: D4T, stavudine; ddI, didanosine; ddC, zalcitabine; Lzd, linezolid; Cs, cycloserine; H, isoniazid; Eto, ethionamide; Pto, protionamide; E, ethambutol; EFV, efavirenz; AZT, zidovudine; RTV, ritonavir; NVP, nevirapine; PAS, *p*-aminosalicylic acid; Z, pyrazinamide; ART, antiretroviral treatment; Cfz, clofazimine; NRTI, nucleoside reverse transcriptase inhibitor; TMP/SMX, trimethoprim/sulfamethoxazole; CMV, cytomegalovirus; ABC, abacavir; 3TC, lamivudine; TDF, tenofovir; Cm, capreomycin; ARV, antiretroviral; IDV, indinavir; R, rifampicin; Rfb, rifabutin; HAART, highly active antiretroviral therapy

*Bristol-Myers Squibb, letter to providers, March 2005

Monitoring of DR-TB and HIV Therapy in Coinfected Patients

HIV treatment must be taken daily without exception to prevent the evolution of drug resistance. Since directly observed therapy (DOT) is an important component of DR-TB therapy, programmes would be advised to explore the provision of TB medications and antiretrovirals (ARVs) through concomitant DOT or other methods of adherence support (see the NGC summary of the WHO guideline, Treatment delivery and community-based DR-TB support). This is particularly important in the setting of second-line antituberculosis therapy, since it can result in a large pill burden and numerous adverse effects that make taking ARVs more difficult.

The complexity of antiretroviral regimens and second-line antituberculosis treatment, each with its own toxicity profiles and some of which may be potentiated by concomitant therapy, demands rigorous clinical monitoring. Table 1 of the NGC summary of the WHO guideline, Initial evaluation, monitoring of treatment and management of adverse effects, describes the monitoring requirements while on DR-TB therapy and indicates where any extra monitoring is required for patients coinfected with HIV and/or on ART.

If the patient shows signs of antituberculosis treatment failure, the same evaluation described in the NGC summary of the WHO guideline, Management of patients after MDR-TB treatment failure, is warranted. In addition, the ART regimen should be evaluated for possible treatment failure, as described in other WHO guidelines.

Given that the regimens together are particularly difficult to take, the stigma of both diseases can result in serious discrimination, and the risk of mortality is very high. Patients with HIV-associated DR-TB may require special socioeconomic, nutritional and psychosocial support in order to successfully complete treatment.

Immune Reconstitution Inflammatory Syndrome

It is important to note that IRIS is a diagnosis of exclusion. Patients with advanced AIDS may show clinical deterioration for a number of other reasons. New opportunistic infections or previously subclinical infections may be unmasked following immune reconstitution and cause clinical worsening. IRIS can also be confused with TB treatment failure, and coinfected patients may be demonstrating progression of TB disease due to drug resistance.

The management of IRIS is complex and depends on the clinical status of the patient and the site and extent of involvement. Various treatment modalities have been employed, including non-steroidal anti-inflammatory drugs in mild disease and corticosteroids in moderate-severe disease. Most patients can be treated without interruption of ART.

XDR-TB and HIV

XDR-TB has been described in a number of countries, including settings with a high prevalence of HIV. An algorithm to help diagnose XDR-TB in HIV-infected individuals is provided in the NGC summary of the WHO guideline, Case-finding strategies. Treatment strategies for XDR-TB are outlined in the NGC summary of the WHO guideline, Treatment strategies for MDR-TB and XDR-TB.

Implications of HIV for MDR-TB Infection Control

Delay in recognition of DR-TB, prolonged periods of infectiousness, crowded wards, and mixing TB and HIV patients all contribute to nosocomial transmission. These practices have contributed to DR-TB outbreaks that affect both HIV-infected and non-infected patients. Implementation of adequate infection control precautions at health facilities significantly reduces nosocomial transmission. Some community-based treatment programmes have used home-based measures such as separate living quarters, personal respiratory protection for visitors and adequate ventilation. Infection control measures for DR-TB, including in the setting of high HIV prevalence, are described in the NGC summary of the WHO guideline, Drug resistance and infection control.

Coordination of HIV and TB Care: Involvement of the TB/HIV Board

The national TB and HIV/AIDS control programmes need a joint strategic plan to collaborate successfully and systematically on carrying out the recommended joint

activities. Given the high prevalence of TB among patients with HIV infection, a joint plan should be made to diagnose TB in such patients, to determine the drug susceptibility of the strain, and to provide adequate and appropriate treatment. Alternatively, components can be introduced in their respective programmes to ensure adequate diagnosis, care, treatment and referral of patients infected with both HIV and DR-TB. Coordinated training activities should focus on developing a group of providers in a specialized multidisciplinary team with adequate expertise in both areas. The roles and responsibilities of each programme at the national and district levels must be clearly defined, as well as the roles of individual team members. Communities and patients should be involved in programme design from an early stage.

Summary

DR-TB in HIV-infected patients is highly lethal and a growing problem in many parts of the world. As programmes embark on DR-TB and HIV control strategies, the activities described in "Recommended Collaborative TB/HIV Activities," above, should be strengthened, and, where absent, implemented. Improved case detection, timely and appropriate therapy, close clinical monitoring, management of adverse effects and infection control measures are the essential components of a successful programme. TB and HIV programmes realizing the control strategies put forth in this chapter will have the best chance to stem the epidemic of HIV-associated DR-TB.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate effective management of drug-resistant tuberculosis (DR-TB) and human immunodeficiency virus (HIV) co-infection

POTENTIAL HARMS

Undue delay in the start of antiretroviral therapy (ART) could result in significant risk of human immunodeficiency virus (HIV)-related death among patients with advanced disease. The optimal timing for the introduction of ART in patients receiving tuberculosis (TB) treatment is unknown.

CONTRAINDICATIONS

CONTRAINDICATIONS

Thioacetazone is contraindicated in human immunodeficiency virus (HIV) because of life-threatening rash.

QUALIFYING STATEMENTS

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IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Chart Documentation/Checklists/Forms
Foreign Language Translations

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

DR-TB and HIV infection. In: World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: World Health Organization (WHO); 2008. p. 89-106. [44 references]

ADAPTATION

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All of the above contributors completed a WHO Declaration of Interest form.

The following interests were declared:

Case Gordon declared that he is an unpaid advocate for patients with anti-TB drug resistance and for improved access to high-quality care. He declared that he has himself survived XDR-TB.

Tim Holtz declared that he is an unpaid technical adviser and member of the Scientific Advisory Board of a manufacturer of anti-TB products, to advise on the development of a new anti-TB compound that will be tested in clinical trials of MDR-TB regimens.

Salmaan Keshavjee declared that his employer received funding from a foundation associated with a manufacturer of anti-TB products to support the research and training unit that he is heading.

Carole Mitnick declared that she is serving as a paid member of the Scientific Advisory Board of a manufacturer of anti-TB products, to advise on the development of a new anti-TB compound that will be tested in clinical trials of MDR-TB regimens.

Michael Rich declared that his employer received funding from a manufacturer of anti-TB products, in support of his salary.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in English, Chinese, and French in Portable Document Format (PDF) from the World Health Organization Web site.

Print copies: Available from the WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; Phone: +41 22 791 3264; Fax: +41 22 791 4857; E-mail: bookorders@who.int.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Executive summary. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: World Health Organization (WHO); 2008. p. xi-xvi. Electronic copies: Available in Portable Document Format (PDF) from the World Health Organization Web site.

Print copies: Available from the WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; Phone: +41 22 791 3264; Fax: +41 22 791 4857; E-mail: bookorders@who.int.

In addition, various forms, registers, and reports are available in the appendices of the original guideline document.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on September 2, 2009. The information was verified by the guideline developer on December 11, 2009.

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